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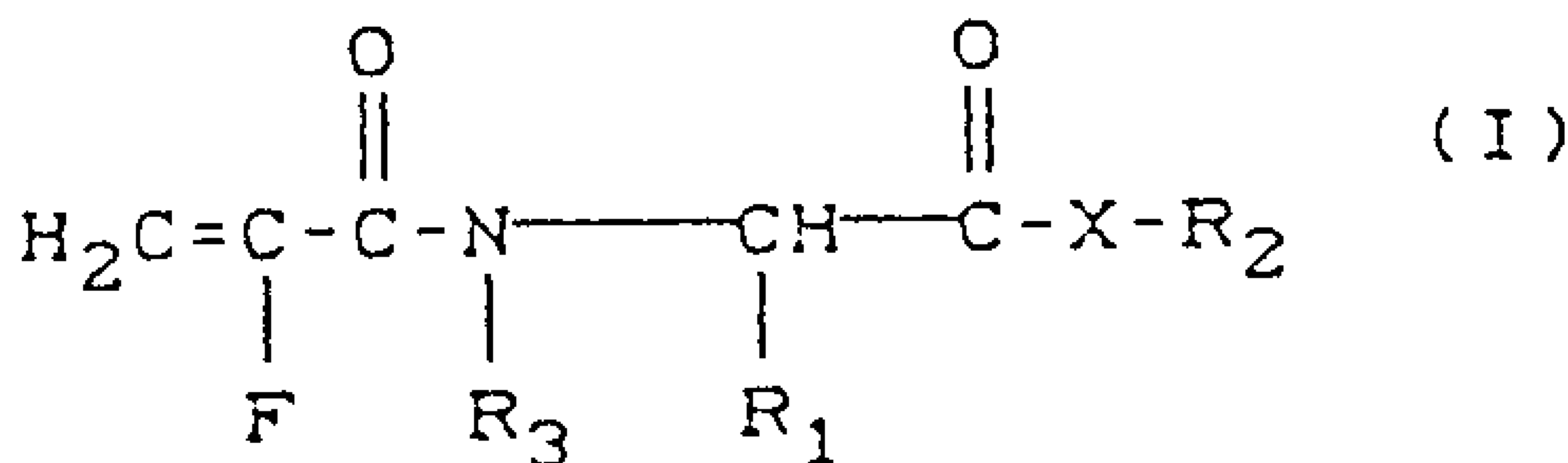
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(54) Titre : DERIVES D'ACIDE N- α -FLUOROACRYLOYLAMINE OPTIQUEMENT ACTIFS ET POLYMERES
OPTIQUEMENT ACTIFS DE CEUX-CI POUR LA RESOLUTION DES RACEMATES

(54) Title: OPTICALLY ACTIVE N- α -FLUOROACRYLOYLAMINO ACID DERIVATIVES AND OPTICALLY ACTIVE
POLYMERS THEREOF FOR THE RESOLUTION OF RACEMATES



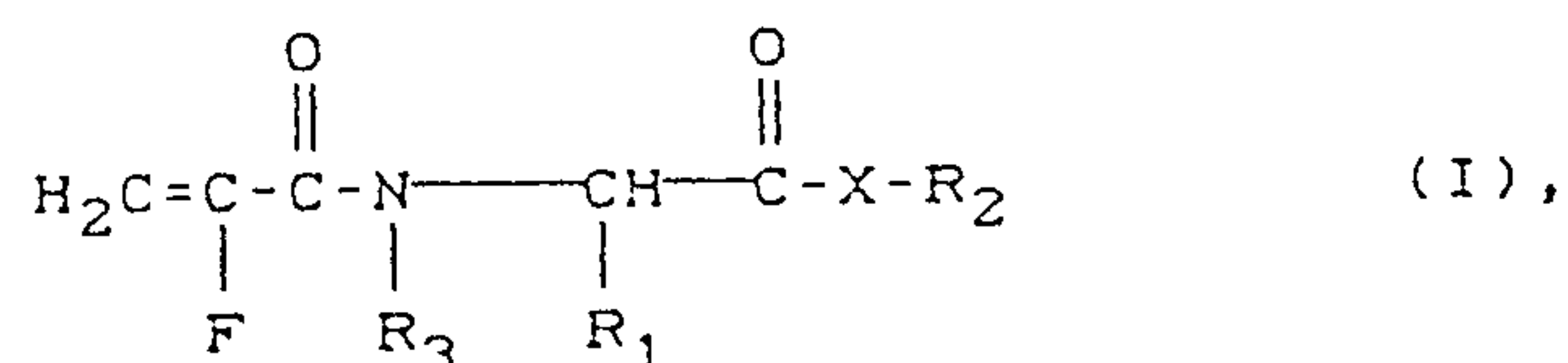
(57) Abrégé/Abstract:

α -Fluoro-substituted N-acryloylamino acid derivatives of the formula (see formula I) are used to make polymers optionally for chromatographic resolution of racemates into their enantiomers. The fluorine atom improves performance in many instances.

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ABSTRACT

α -Fluoro-substituted N-acryloylamino acid derivatives
of the formula



are used to make polymers optionally for
chromatographic resolution of racemates into their
enantiomers. The fluorine atom improves performance in
many instances.

The invention relates to novel optically active N- α -fluoroacryloylamino acid derivatives, to a process for their preparation, to their polymerization to give optically active polymers and to the use of these optically active polymers as adsorbents for the chromatographic resolution of racemates into their enantiomers.

In recent years, the resolution of racemates of active compounds has become increasingly important, since it has been shown that the enantiomers of the racemate of an active compound often differ in their biological effects and side effects.

Apart from the classic methods for the resolution of racemates, chromatographic resolution of racemates has proved particularly suitable in recent times. Apart from natural product derivatives, for example based on cellulose, synthetic optically active poly(meth)acrylamides have increasingly been used as adsorbents (Review: G. Blaschke, Chromatogr. Sci. 1988, 40, 179-198).

However, when applying the known methods, it was found that they either have an inadequate effect or only have an efficiency which is limited to certain racemates.

Surprisingly, it has now been found that polymers made of optically active α -fluoroacrylamides of amino acid esters or amino acid amides are adsorbents with very good

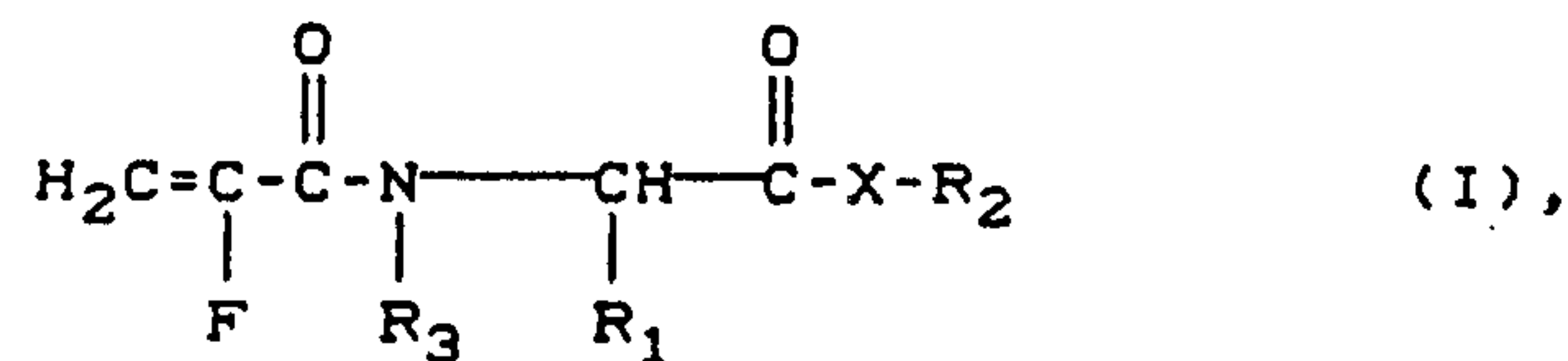
racemate-resolving properties.

Surprisingly, the substitution of the hydrogen atom or the methyl group in the (meth)acrylamides by the strongly electronegative fluorine atom does not lead to a loss in separation efficiency, as would be expected owing to the opposite electronic effect and the vicinity of the fluorine atom to the amide group, which, as is known, has to interact with the enantiomers of the racemate to be resolved via hydrogen bridges.

Rather, it is observed that racemates which pass through the corresponding poly(meth)acrylamide adsorbent unresolved can in many cases be resolved into enantiomers by the novel polyfluoroacrylamides of this type.

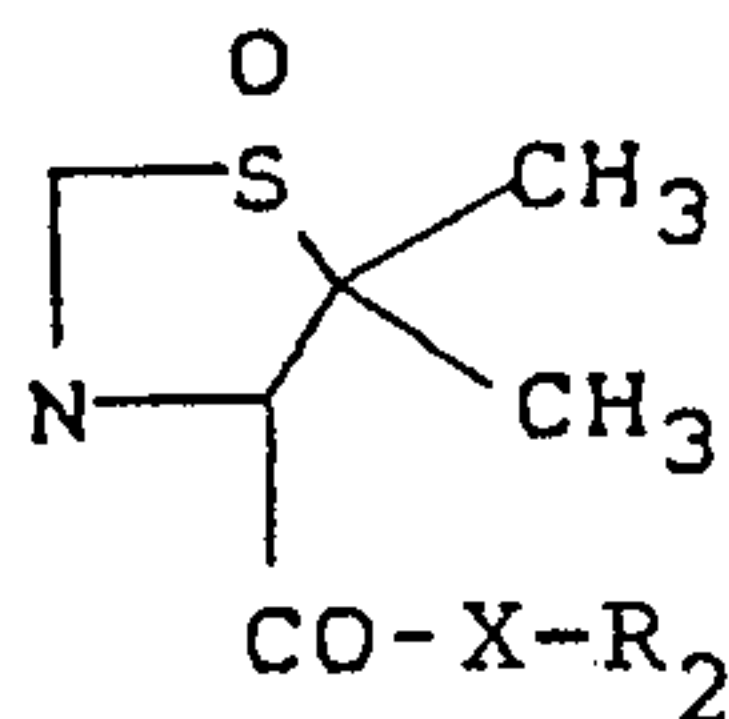
Thus, the polyfluoroacrylic acid derivatives according to the invention unexpectedly give rise to adsorbents for the chromatographic resolution of racemates, whose properties differ significantly from those of the corresponding (meth)acrylamides.

The invention relates to N- α -fluoroacryloylamino acid derivatives of the formula (I)



in which

- 5 R_1 represents a straight-chain or branched C_1-C_8 -alkyl, a C_7-C_{12} -aralkyl, a C_3-C_{10} -cycloalkyl, a C_6-C_{14} -aryl or a furyl, thienyl or pyridyl radical, which are unsubstituted or substituted by benzyloxycarbonyl, alkoxycarbonyl of up to 6 C atoms, hydroxyl, alkyl, cycloalkyl or alkoxy each having up to 6 C atoms, halogen, phenoxy, benzoxy, acylamino of up to 8 C atoms or by carbonylalkoxy of up to 6 C atoms,
- 10 R_3 represents hydrogen or C_1-C_4 -alkyl or together with R_1 forms a tri- or tetramethylene group,
- X is oxygen or an NR_4 group, in which
 15 R_4 represents hydrogen or straight-chain or branched C_1-C_4 -alkyl or together with R_2 and the nitrogen atom forms a 5- to 7-membered ring which is unsubstituted or substituted by an alkoxycarbonyl group of up to 6 carbon atoms or by one or two alkyl groups each having 1 to 4 carbon atoms,
- 20 R_2 represents a straight-chain or branched C_1-C_{22} -alkyl, C_7-C_{12} -aralkyl, C_3-C_{10} -cycloalkyl, C_6-C_{14} -aryl or a terpenyl radical, each of which is unsubstituted or substituted by halogen, alkyl or alkoxy each having 1 to 4 C atoms, or
- R_1 together with the group $X-R_2$ represents the radical



Examples of suitable substituted or unsubstituted
 straight-chain or branched C_1 - C_8 -alkyl as radicals R_1 are
 methyl, ethyl, i-propyl, n-propyl, n-butyl, i-butyl,
 5 t-butyl, 1-hydroxymethyl, 1-hydroxyethyl, 3-acetylamino-
 propyl, 4-benzoylaminoethyl, t-butoxymethyl, benzyloxy-
 methyl, 2-methoxycarbonylmethyl, 3-methoxycarbonylethyl,
 4-t-butoxycarbonylpropyl or, for example, 2-cyclohexyl-
 ethyl; examples of substituted or unsubstituted
 10 C_7 - C_{12} -aralkyl are benzyl, 1-naphthylmethyl,
 2-naphthylmethyl, 3-indolylmethyl, 4-hydroxybenzyl,
 2-phenylbutyl, 3-phenylbutyl and 4-phenylbutyl; examples
 of substituted or unsubstituted straight-chain or
 branched C_4 - C_{10} -cycloalkyl are cyclopropyl, cyclobutyl,
 15 cyclopentyl, cyclohexyl or decahydronaphthyl; examples of
 substituted or unsubstituted C_6 - C_{14} -aryl are phenyl,
 1-naphthyl and 2-naphthyl.

Examples of radicals R_4 are hydrogen, methyl, ethyl,
 n-propyl, i-propyl, n-butyl and i-butyl, while examples
 20 of a substituted or unsubstituted ring are pyrrolidinyl,
 piperidinyl, morpholinyl, 2-alkoxycarbonylpyrrolidinyl
 and 2-alkoxymethylpyrrolidinyl each having 1 to 4 C atoms

in the alkoxy group.

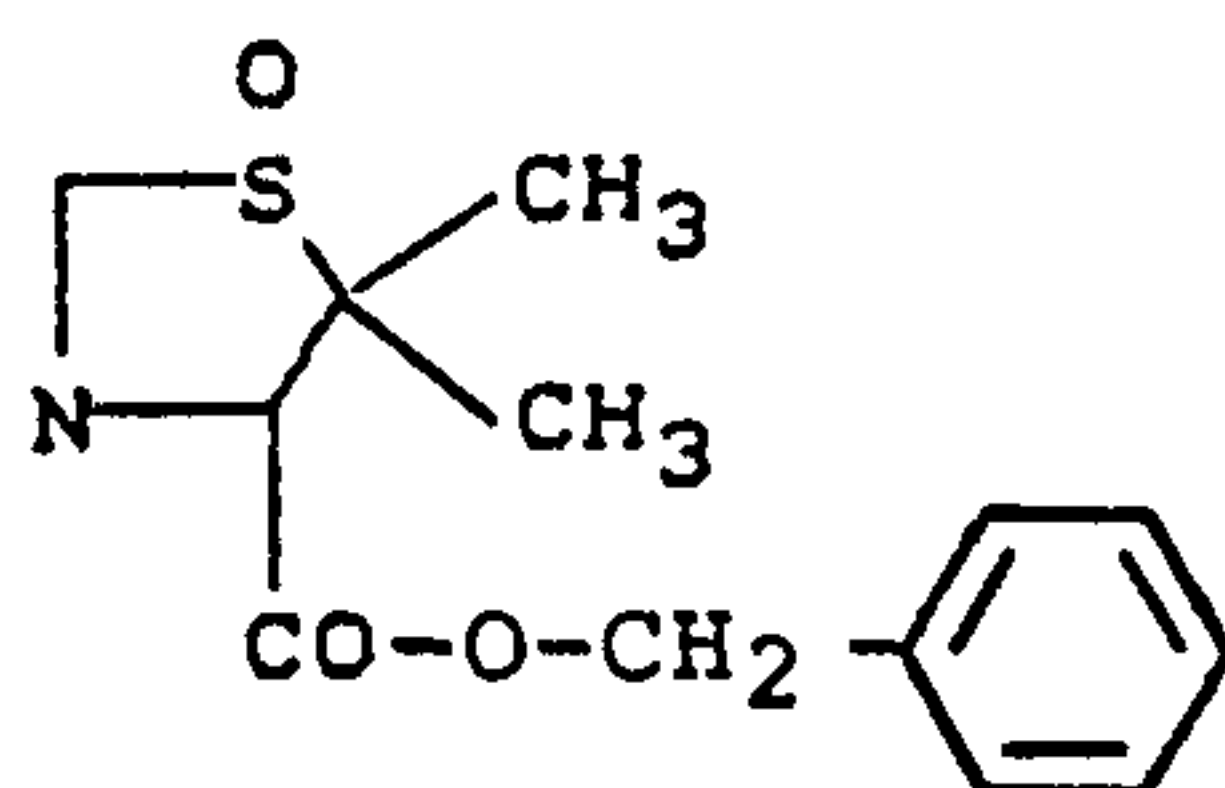
Examples of radicals R_2 are unsubstituted or halogen- or alkoxy-(C_1-C_4)-substituted straight-chain or branched C_1-C_{22} -alkyl radicals, such as methyl, ethyl, trifluoroethyl, 2-chloroethyl, n-propyl, i-propyl, hexafluoroisopropyl, 2-methoxyethyl, 2-t-butoxyethyl, n-butyl, i-butyl, t-butyl, 2-octyl, 2-nonyl, stearyl and behenyl; substituted or unsubstituted C_7-C_{12} -aralkyl radicals, such as benzyl, 1-phenylethyl and 1-naphthylethyl; unsubstituted or halogen-, alkoxy-(C_1-C_4)- or alkyl-(C_1-C_4)-substituted C_4-C_{10} -cycloalkyl radicals, such as cyclobutyl, cyclopentyl, cyclohexyl, 2,6-dimethylcyclohexyl, 3,5-dimethylcyclohexyl, 4-t-butylcyclohexyl or decahydronaphthyl; unsubstituted or halogen-, alkoxy-(C_1-C_4)- or alkyl-(C_1-C_4)-substituted C_6-C_{14} -aryl radicals, such as phenyl and 1-naphthyl and 2-naphthyl; furthermore racemic or advantageously optically active terpenyl radicals, such as menthyl, 8-phenylmenthyl, neomenthyl, isomenthyl, bornyl, fenchyl, pinanyl and isopinocamparyl. Chiral radicals R_2 can be used in racemic form or advantageously in optically active form.

Compounds of the general formula (I) in which

R_1 represents alkyl of 1 to 4 C atoms, benzyl, cycloalkyl of 3 to 7 C atoms, phenyl, indolylmethyl, naphthyl, naphthylmethyl, furyl, thienyl or pyridyl, in which the alkyl and aryl radicals mentioned are unsubstituted or mono- or disubstituted by hydroxyl,

methoxy, halogen, alkyl, cycloalkyl of up to 6 C atoms, phenoxy, benzoxy, acetylamino, benzyloxy-carbonyl or alkoxycarbonyl of up to 4 C atoms,

- 5 R_3 represents hydrogen, methyl or ethyl or together with R_1 forms a tri- or tetramethylene group,
- 10 X represents oxygen or an NR_4 group, in which R_4 represents hydrogen or alkyl of 1 to 4 C atoms or together with R_2 and the nitrogen atom forms a 5- to 7-membered ring which is unsubstituted or substituted by alkyl or alkoxycarbonyl each having up to 4 C atoms, and
- 15 R_2 represents alkyl of up to 12 C atoms, benzyl, cycloalkyl of 3 to 7 C atoms, phenyl or terpenyl, in which the radicals mentioned are unsubstituted or substituted by fluorine, chlorine or bromine or by alkyl or alkoxy each having up to 2 C atoms, or
- R_1 together with the group $X-R_2$ represents the radical

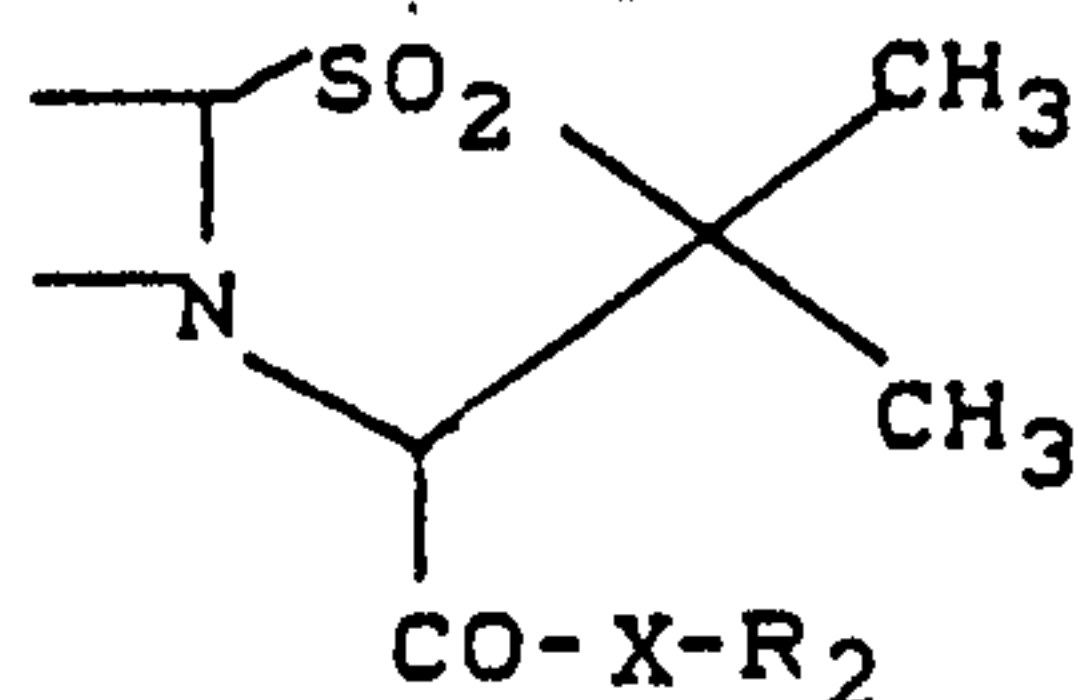


are of particular interest.

The optically active N- α -fluoroacryloylamino acid derivatives, according to the invention, of the formula (I) are preferably derived from optically active amino acids, such as alanine, aminobutyric acid, valine, norvaline, leucine, isoleucine, terleucine, phenylglycine, naphthylglycine, phenylalanine, thienylalanine, pyridylalanine, naphthylalanine, cyclohexylglycine, cyclohexylalanine, tyrosine, tryptophan, serine, aspartic acid, glutamic acid, ornithine, lysine, proline or 6-aminopenicillanic acid, i.e. R^1 preferably represents alkyl of 1 to 4 C atoms, benzyl, cyclohexyl, phenyl, indolylmethyl, naphthyl, naphthylmethyl, thienyl or pyridyl, in which the alkyl and aryl radicals mentioned may be unsubstituted or monosubstituted by hydroxyl, phenoxy, benzoxy, acetylamino, benzyloxycarbonyl or alkoxycarbonyl of up to 4 C atoms, or

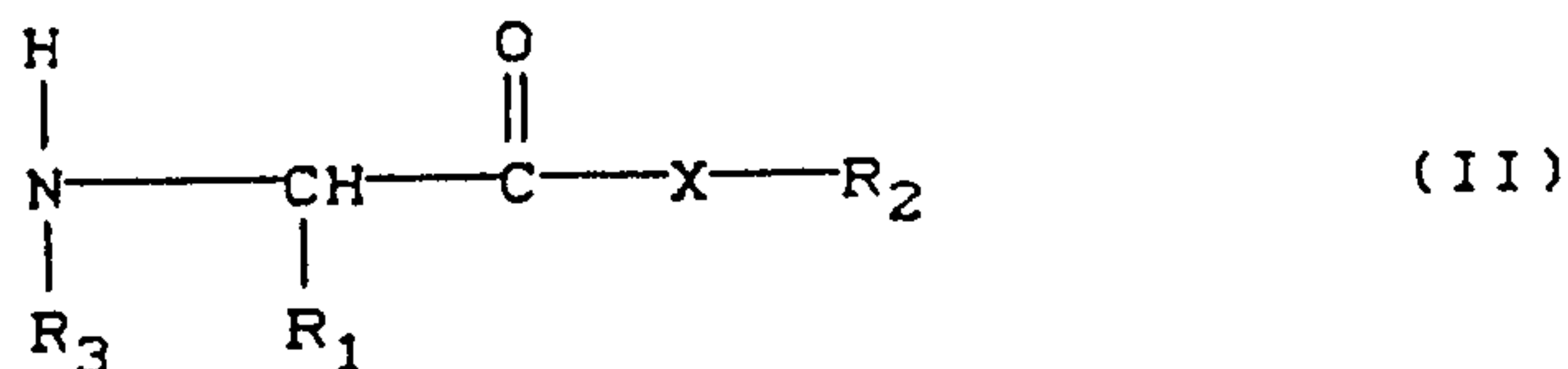
R_1 together with R_3 forms a trimethylene group which is substituted by C₁-C₄-alkoxycarbonyl or

R_1 together with X- R_2 forms the radical



The optically active N-fluoroacryloylamino acid derivatives, according to the invention, of the formula (I) are obtained either

- A) by reaction of optically active amino acid derivatives of the formula



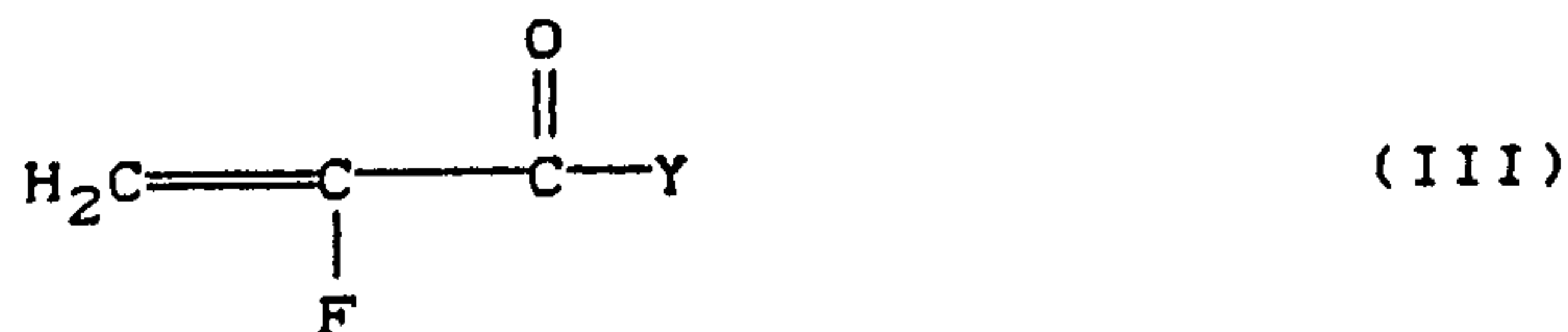
in which

R_1 , R_2 and R_3 are as defined under formula (I),

5

or their acid addition products,

with fluoroacryloyl derivatives of the formula



in which

Y represents fluorine, chlorine or bromine,

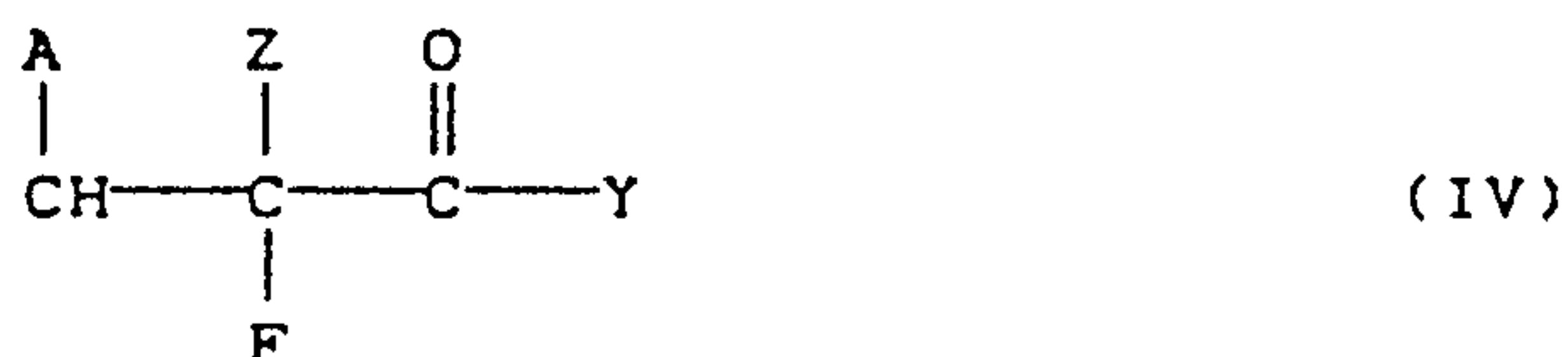
if appropriate in the presence of an acid-binding agent in inert organic solvents,

10

or

- B) by reaction of compounds of the formula (II) with a

fluorine compound of the formula



in which

Y is as defined above, and

5 A and Z each represent hydrogen, fluorine, chlorine
or bromine, in which A and Z never simul-
taneously denote hydrogen, thus enabling the
fluoroacryloyl compound (III) to be
liberated by elimination of AZ, in which AZ
is preferably HF, HCl, HBr, Br₂ or Cl₂.

10 α-Fluoroacryloyl derivatives of the formula (III) or
precursors thereof (IV) can be prepared by processes
known per se [Zh. Org. Khim. 28, 1173 (1983)] and can, if
desired, also be used in the form of acid anhydrides.

15 The optically active amino acid esters of the formula
(II) used as starting compounds are known or can be
prepared by processes known per se (see Bull. Chem. Soc.
Jap. 37 (1964), 191).

20 Suitable acid addition compounds of the amino acids to be
used as starting compounds are salts of these amino acids
with inorganic or organic acids. Mineral acids, such as
hydrochloric acid, hydrobromic acid, sulphuric acid,

phosphoric acid or organic acids, such as acetic acid, methane-, ethane-, benzene- or toluenesulphonic acid, are preferred.

5 Suitable solvents are all organic solvents which are inert under the reaction conditions. Hydrocarbons, such as benzene, toluene, xylene, or petroleum fractions, or halogenated hydrocarbons, such as di-, tri- or tetra-
10 chloromethane, dichloroethane or trichloroethylene, or ethers, such as tert.-butyl methyl ether or tert.-amyl ethyl ether are preferred.

15 Suitable acid-binding agents are in particular the customary inorganic or organic bases; alkali metal hydroxides or alkaline earth metal hydroxides, such as sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide or barium hydroxide, alkali metal
20 carbonates or alkaline earth metal carbonates, such as sodium carbonate or potassium carbonate or sodium bicarbonate, alkali metal alcoholates, such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium t-butoxide, or amines, such as triethylamine or pyridine, are preferably used.

25 The reaction of the α -fluoroacryloyl derivatives of the formula (III) with the amino acid derivatives of the formula (II) is preferably carried out at temperatures of -78 to +100°C, in particular -20°C to +60°C.

The invention also relates to the optically active

diameter of 5 to 200 μm . They are prepared, for example, by suspension polymerization of the optically active N- α -fluoroacryloylamino acid derivatives of the formula (I) with 0.5 to 50 mol%, preferably 1 to 30 mol%, particularly preferably 3 to 20 mol%, (relative to the total amount [mol] of the monomers used), of a suitable cross-linking agent in a manner known per se.

The degree of swelling of the (bead) polymers can be adjusted by conventional methods via the type and amount of the crosslinking agents.

In practical use, (bead) polymers having a degree of swelling (Q) of 1.1 to 10, preferably 2.0 to 7.0, have proved suitable.

The degree of swelling Q is determined as follows:

$$Q = \frac{\text{polymer volume (swollen)}}{\text{polymer volume (unswollen)}}$$

Suitable crosslinking agents are compounds containing at least two polymerizable vinyl groups. Preferred cross-linking agents are alkanediol diacrylates, such as 1,6-hexanediol diacrylate, 1,4-butanediol diacrylate, 1,3-propanediol diacrylate or 1,2-ethylene glycol diacrylate, or alkanediol methacrylates, such as 1,4-butanediol dimethacrylate, 1,3-butanediol dimethacrylate, 2,3-butanediol dimethacrylate, 1,3-propanediol dimethacrylate or 1,2-ethylene glycol dimethacrylate, aromatic

divinyl compounds, such as, for example, divinylbenzene, divinylchlorobenzene or divinyltoluene, vinyl dicarboxylates, such as divinyl adipate, divinyl benzene dicarboxylate, divinyl terephthalate, N,N'-alkylenediacrylamides, such as N,N'-methylenediacrylamide, N,N'-ethylenediacrylamide, N,N'-methylenedimethacrylamide or N,N'-ethylenedimethacrylamide.

Suitable free-radical formers are the conventional free-radical formers. Peroxides, such as, for example, dibenzoyl peroxide, dilauroyl peroxide or di-ortho-tolyl peroxide, or azo compounds, such as, for example, azobisisobutyronitrile (AIBN) are preferred. Mixtures of various free-radical formers can also be used.

The polymerization components are dissolved in an organic solvent which is not miscible with water, preferably an aliphatic or aromatic hydrocarbon, such as hexane, heptane, isododecane, benzene or toluene, a halogenated hydrocarbon, such as di-, tri-, tetrachloromethane or 1,2-dichloroethane or an ester, such as ethyl acetate or butyl acetate.

The organic phase is evenly distributed in the aqueous solution of a protective colloid, preferably in an aqueous solution of polyvinyl alcohol, polyvinylpyrrolidone or a copolymer consisting of methacrylic acid and methyl methacrylate, by means of an efficient stirrer. About 1 to 20, preferably 2 to 10, parts by weight of aqueous phase are used per part by weight of

organic phase. The polymerization mixture is heated in an inert gas atmosphere, preferably under nitrogen, to temperatures of 30°C to 150°C, preferably 40°C to 80°C, with stirring. The polymerization time is 2 to 24, preferably 4 to 12, hours. The copolymer obtained in this manner is separated from the liquid phase by filtration, purified by thorough washing with water and with organic solvents, such as methanol, ethanol, benzene, toluene, di- or trichloromethane or acetone, and then dried.

10 In particular for analytical applications, the optically active polymers according to the invention are preferably used in a form in which they are bound to finely divided inorganic supports. The preparation of optically active chromatographic phases of this type can be carried out, 15 for example, by the processes described in DE-A-3,706,890.

Preference is given to the polymerization of the optically active N- α -fluoroacryloylamino acid derivatives of the formula (I) in the presence of vinyl/silica gels or 20 silical gel/diol phases esterified with (meth)acrylic acid. This polymerization can be carried out in the absence of solvents or in the presence of solvents or precipitants for poly-N- α -fluoroacrylamides. The free-radical formers used for the preparation of the bead 25 polymers can also be used as initiators.

The polymer-modified silica gels preferably contain 1 to 40% by weight, in particular 5 to 30% by weight, of

optically active polymer (V), relative to the total weight. They are thoroughly washed with solvents for the polymer and dried in vacuo.

5 It is of course also possible here to use mixtures of two or more of the N- α -fluoroacryloylamino acid derivatives according to the invention, if appropriate also together with further copolymerizable monomers.

10 The invention furthermore relates to the use of the poly-N- α -fluoroacrylamides, according to the invention, of the formula (V) as such or in crosslinked or silica gel-bound form for the chromatographic resolution of racemic mixtures into the optical antipodes. Examples of readily resolvable racemates are oxazepam, binaphthol, benzoin, chlorothalidone, thalidomide, N-3,5-dinitrobenzoyl-
15 leucine, 1-(9-anthryl)2,2,2-trifluoroethanol and tetrahydro- and hexahydrocarbazole derivatives, such as, for example, 3-(4-chlorophenylsulphonamido)-9-(2-carboxyethyl)1,2,3,4-tetrahydrocarbazole, 3-r-(benzene-sulphonamido)-9-(2-carboxyethyl)-1,2,3,4,4a,9a-hexahydro-
20 carbazole, 1-(carboxymethyl)-6-fluoro-9-(4-chlorobenzyl)-1,2,3,4-tetrahydrocarbazole, hydroxyalkylazole derivatives, such as, for example, 2-(4-chlorophenyl)-3-methoxyimino-3-methyl-1-(1,2,4-triazol-1-yl)-2-butanol and α -(4-fluorophenyl)- α -(1-cyanocyclopropyl)-1H-(1,2,4-
25 triazol-1-yl)-ethanol and 1,4-dihydropyridine derivatives, such as, for example, 5-monoethyl 1,4-dihydro-2,6-dimethyl-4-(2-trifluoromethylphenyl)-3,5-dicarboxylate.

The composition of the eluent can be selected in the usual manner and optimized, depending on the type and the property of the racemate to be resolved. The poly-N- α -fluoroacryloylamino acid derivatives according to the invention which are bound to silica gel can be used for resolutions of racemates under HPLC conditions.

The capacity of the polymers for the resolution of racemates is expressed in terms of the capacity ratios ($k'_{1(2)}$ values) for the two enantiomers (1) and (2) and the resulting enantioselectivity value α . These chromatographic parameters are defined as follows:

$$\text{Capacity ratio } k_{1(2)} = \frac{t_{1(2)} - t_0}{t_0}$$

$$\text{Enantioselectivity } \alpha = \frac{k'_2}{k'_1}$$

t_0 = dead time of the column

$t_{1(2)}$ = retention time of the first eluted enantiomer 1 or of the later eluted enantiomer 2

The preparative resolution of racemic mixtures into their optical antipodes using the polymers according to the invention is preferably carried out by column chromatography. This is particularly advantageously done by carrying out the chromatographic separation using bead polymers of a definite particle size distribution; good separation efficiencies are obtained with bead polymers of a particle size distribution of 5 to 200 μm ,

preferably 15 to 100 μ m.

The operating procedure of separation by column chromatography is known. Usually, the polymer is suspended in the eluent, and the suspension is poured into a glass column. After the eluent has been drained, the racemate to be resolved is applied to the column as a solution in the minimal amount of eluent. It is then eluted using the eluent, and the enantiomers in the eluate are detected by photometry and/or polarimetry by means of suitable flow cells.

The eluents used are conventional organic solvents or solvent mixtures which swell the polymer used as the adsorbent and dissolve the racemate to be resolved. Examples are: hydrocarbons, such as benzene, toluene or xylene, ethers, such as diethyl ether, t-butyl methyl ether, dioxane or tetrahydrofuran, halogenated hydrocarbons, such as di- or trichloromethane, acetone, acetonitrile or ethyl acetate, alcohols, such as methanol, ethanol, n-propanol, isopropanol or n-butanol, or else mixtures of the solvents mentioned. Mixtures of toluene with tetrahydrofuran, dioxane or isopropanol have proved particularly suitable.

The invention will be further described hereinbelow with reference to the accompanying drawings wherein

Figs. 1 to 9 are chromatograms showing elution times in minutes on the horizontal axis and concentration of active material in the eluate vertically, for different racemates and adsorbents in accordance with the present invention.

ExamplesI. Preparation method of N- α -fluoroacryloylamino acid derivatives (monomers)

Method a) starting from 2,3-difluoropropionyl chloride

5

A solution of 0.2 mol of 2,3-difluoropropionyl chloride in 200 ml of anhydrous dichloromethane is initially introduced, 0.205 mol of triethylamine is added dropwise at 0°C, and the mixture is stirred at 0°C for 30 minutes.

10

A mixture of 0.2 mol of the amino acid derivative and 0.2 mol of triethylamine in 200 ml of anhydrous dichloromethane is then added dropwise to this solution at -10°C.

The mixture is allowed to reach room temperature and then subjected to aqueous work up as usual.

15

Method b) using α -fluoroacryloyl chloride

20

First 0.2 mol of triethylamine is added dropwise at 0°C to a solution of 0.1 mol of an amino acid ester or amide hydrochloride of the formula (II) in 300 ml of dichloromethane, followed by dropwise addition of a solution of 0.1 mol of α -fluoroacryloyl chloride in 25 ml of dichloromethane at -10°C. The mixture is stirred for 30 minutes without cooling, washed in succession with water, 1N HCl and saturated NaHCO₃ solution, dried over magnesium sulphate and freed from the solvent on a rotary evaporator. The product obtained after drying in a high vacuum is recrystallized or purified by chromatography on silica gel.

25

If a free amino acid ester or amide is used, the amount of triethylamine is reduced to half. The N- α -fluoroacryloylamino acid derivatives thus prepared are listed in Table I.

Table I Optically active monomers (I)

Example No.	N- α -fluoroacryloylamino acid derivative	Preparation method	M.p. (°C)	Angle of rotation (C=1, CHCl ₃)	Yield (% of theory)
1	N-fluoroacryloyl-L-phenylalanine ethyl ester	a	36°C	+112°	65
2	N-fluoroacryloyl-L-phenylalanine n-propyl ester	a	31°C	+103°	73
3	N-fluoroacryloyl-L-phenylalanine i-propyl ester	a	82°C	+106.9°	78
4	N-fluoroacryloyl-L-phenylalanine t-butyl ester	b	71°C	+103.2°	89
5	N-fluoroacryloyl-L-phenylalanine d-menthyl ester	b	oil	+85.4°	63
6	N-fluoroacryloyl-L-alanine d-menthyl ester	b	34°C	+55.8°	83
7	N-fluoroacryloyl-L-alanine l-bornyl ester	b	80°C	-38.1°	80
8	N-fluoroacryloyl-L-alanine (+)-fenchyl ester	b	oil	+36.4°	83
9	N-fluoroacryloyl-L-leucine t-butyl ester	b	47°C	+3.1°	83
10	N-fluoroacryloyl-D-phenylglycine t-butyl ester	b	117°C	-176.8°	64

II. Polymerization of the N- α -fluoroacryloylamino acid derivatives (I)

1. Preparation in the silica gel-bound form

- 5 a) 25 g of silica gel modified with 1,2-diol groups (average particle size: 5 μ m) are suspended in 500 ml of dioxane with the exclusion of moisture and under nitrogen. 16 ml of methacrylic anhydride and 12.5 ml of triethylamine are added to the suspension. The mixture is stirred at room temperature for 10 1 hour and stored at room temperature for 24 hours. The silica gel is then filtered off with suction through a sintered glass crucible (G4), stirred 3 times with 500 ml each of dioxane for 30 minutes, and sucked thoroughly dry in between. The silica gel 15 modified with methacryloyl groups is dried at room temperature in a vacuum at <0.005 atm.

Yield 24.8 g

Elemental analysis: C: 9.2%; H: 1.7%

Values of the silica gel modified with diol groups:

20 C: 7.7%; H: 1.5%

- 25 b) 3 g of the silica gel modified with methacryloyl groups, the preparation of which is described under a), 6.0 g of optically active N- α -fluoroacryloylamino acid derivative and 60 mg of azobisisobutyronitrile are dissolved or suspended in 25 ml of dry toluene in a 100 ml round-bottom flask equipped with

reflux condenser and magnetic stirrer. The apparatus is freed from air by evacuating it and filling it with nitrogen three times, and then filled with nitrogen. The polymerization mixture is stirred at room temperature for 1 hour and then rapidly heated to 80°C. After stirring at 80°C for 45 minutes, 200 mg of 2,6-di-tert.-butyl-4-methylphenol are added, and the reaction mixture is rapidly cooled. The silica gel is filtered off with suction through a sintered glass crucible (G4), washed with toluene and stirred twice with 50 ml each of chloroform, once with 50 ml of toluene and once with 50 ml of isopropanol for 30 minutes each and filtered off with suction in between. The silica gel is finally dried at room temperature in vacuo at <0.005 atm. In Table II below, the N- α -fluoroacryloylamino acid derivatives polymerized onto the modified silica gel, the yields of silica gel containing optically active compounds, its nitrogen content and its bound polymer content are summarized.

- c) In the apparatus described under b), 3.0 g of the silica gel modified with methacryloyl groups, the preparation of which is described under a), 6.0 g of optically active N- α -fluoroacryloylamino acid derivative and 60 mg of azobisisobutyronitrile are dissolved or suspended in 25 ml of dry trichloromethane. The apparatus is freed from air by alternate evacuation and filling with nitrogen three times, and finally filled with nitrogen. The

5 reaction mixture is stirred at room temperature for
1 hour and under reflux for 1 hour. After addition
of 200 mg of 2,6-di-tert.-butyl-4-methylphenol, the
batch is rapidly cooled. The silica gel is filtered
off with suction through a sintered glass crucible
(G4), stirred twice with 50 ml each of chloroform,
once with 50 ml of toluene and once with 50 ml of
isopropanol for 30 minutes each and filtered off
with suction in between. The silica gel is finally
10 dried at room temperature in vacuo at <0.005 atm.

Table II Optically active polymers (V) on silica gel

Ex. No.	N- α -fluoroacryloylamino acid derivative according to Ex.	Preparation procedure	Yield (g)	[N-content] (%)	Silica gel-bound polymer content (% by weight)
11	1	1b	3.3	1.0	18.9
12	2	1c	3.3	0.75	15.0
13	3	1b	3.15	0.7	14.0
14	4	1b	3.35	0.75	15.7
15	5	1b	3.15	0.55	14.8
16	6	1b	3.1	0.65	13.9
17	7	1b	3.25	0.75	15.9
18	8	1b	3.4	0.65	13.8
19	9	1b	3.05	0.7	13.0
20	10	1b	3.1	0.9	18.0

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2. Preparation in the form of bead polymers

A solution of 13.5 g of optically active N- α -fluoroacryloylamino acid derivative, 1.5 g of ethylene glycol dimethacrylate and 0.3 g of azobisisobutyronitrile in
5 37.5 g of trichloromethane is dispersed in a solution of
3 g of polyvinyl alcohol in 130 ml of deionized water,
with stirring. The apparatus is evacuated several times
and filled with nitrogen. The polymerization mixture is
10 stirred first at room temperature for 30 minutes under
nitrogen and then at 55°C (internal temperature) for 16
hours. The polymerization mixture is then stirred into 2
to 3 l of water, and the liquid phase is decanted, after
the bead polymer has settled. The bead polymer is freed
15 from the fines (polymer having a particle size of $<10\ \mu\text{m}$)
by suspending it in water and decanting the liquid phase
3 to 4 times, and, after thorough washing with acetone,
dried to constant weight at 60°C.

In Table III below, the N- α -fluoroacryloylamino acid
derivatives used for the polymerization, the stirring
20 rate at which the polymerization was carried out, the
yields in which the polymers were obtained, the particle
size thereof and the volume of the bead polymers obtained
in a dry (V_{dry}) and swollen (V_s) state (swelling agent:
toluene = T or toluene/THF 3:2 v/v mixture = T/T) are
25 summarized.

Table III Optically active polymers (V) as bead polymers

Ex. No.	N-fluoroacryloylamino acid derivative according to Example	Stirring rate [rpm]	Yield of beads >10 μ m (g)	Particle size of the beads (μ m)	V_{us} (ml/g)	V_s (ml/g)	Swelling agent
21	1	500	9.8	15-80	1.8	5.5	T
22	2	450	9.2	15-70	2.1	5.7	T
23	3	350	11.7	20-120	1.6	5.5	T
24	4	400	12.3	20-110	1.6	5.2	T
25	5	400	12.1	15-80	1.6	6.0	T/T
26	6	400	12.4	15-80	1.7	5.7	T
27	7	450	11.8	15-85	2.3	5.5	T/T
28	8	450	11.6	15-80	1.8	5.6	T/T
29	9	450	12.2	15-75	1.9	6.3	T/T
30	10	450	12.0	20-110	1.6	4.8	T

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III. Use of the N- α -fluoroacryloylamino acid derivatives
(I) as adsorbents for the resolution of racemates

The following test racemates were used for the chromatographic resolutions as shown in the drawings:

- 5 Racemate No. 1: Oxazepam
Racemate No. 2: Binaphthol
Racemate No. 3: Chloro~~o~~thalidone
Racemate No. 4: Thalidomide
Racemate No. 5: N-3,5-dinitrobenzoylleucine
10 Racemate No. 6: 3-r-(benzenesulphonamido)-9-(2-carboxy-ethyl)-1,2,3,4,4a,9a-hexahydrocarbazole

15 The silica gel-bound polymers were used in steel columns (inner diameter: 4 mm, length: 25 cm). n-Heptane/tetrahydrofuran 3:2 mixtures = eluent a, 1:1 = eluent b, 1:2 = eluent c, were used as eluents; the eluent rate was 1 ml/min.

20 The chromatograms shown below demonstrate the surprisingly good separation efficiency of the polymers according to the invention. The abscissa shows the elution time in minutes. Detection was carried out by UV absorption.

25 By comparison with the polymers according to the invention, it was sought to resolve the test racemates 2 and 4 in eluent a and the test racemate 3 in eluent b on a silica gel column covered with N-acryloylphenylalanine

ethyl ester (Chiraspher® from Merck). In all cases, upon UV detection, no enantiomer resolution was observed, and the enantioselectivity α was 1.00, although the polymer used differed from the polymer of Example 11 only through the missing fluorine substitution.

Figure 1

Racemate No. 1

Adsorbent according to Example 17

Eluent: a

Figure 2

Racemate No. 2

Adsorbent according to Example 11

Eluent: a

Figure 3

Racemate No. 2

Adsorbent according to Example 16

Eluent: a

Figure 4

Racemate No. 3

Adsorbent according to Example 11

Eluent: b

Figure 5

Racemate No. 4

Adsorbent according to Example 11

Eluent: c

Figure 6
Racemate No. 4
Adsorbent according to Example 18
Eluent: a

5 Figure 7
Racemate No. 5
Adsorbent according to Example 17
Eluent: a

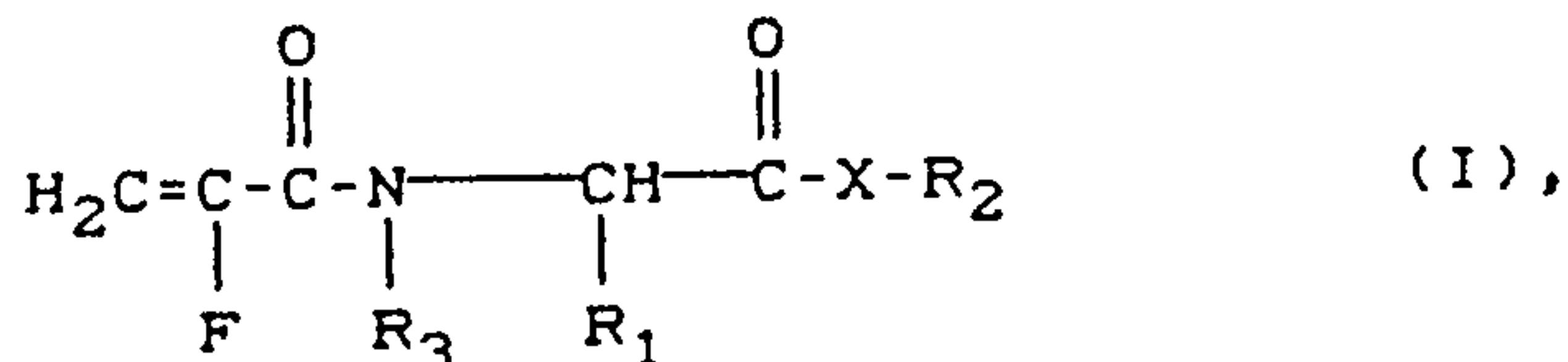
10 Figure 8
Racemate No. 6
Adsorbent according to Example 16
Eluent: a

15 Figure 9
Racemate No. 6
Adsorbent according to Example 18
Eluent: a

It will be understood that the specification and examples are illustrative but not limitative of the present invention and that other embodiments within the spirit and scope of the invention will suggest themselves to those skilled in the art.

Patent claims

1. An N- α -fluoroacryloylamino acid derivative of the formula (I)



in which

- 5 R_1 represents a straight-chain or branched C_1 - C_8 -alkyl, a C_7 - C_{12} -aralkyl, a C_3 - C_{10} -cycloalkyl, a C_6 - C_{14} -aryl or a furyl, thienyl or pyridyl radical, which are unsubstituted or substituted by benzyloxycarbonyl, alkoxy carbonyl of up to 6 C atoms, hydroxyl, alkyl, 10 cycloalkyl or alkoxy each having up to 6 C atoms, halogen, phenoxy, benzoxy, acylamino of up to 8 C atoms or by carbonylalkoxy of up to 6 C atoms,
- R_3 represents hydrogen or C_1 - C_4 -alkyl or together with R_1 forms a tri- or tetramethylene group,
- 15 X is oxygen or an NR_4 group, in which
- R_4 represents hydrogen or straight-chain or branched C_1 - C_4 -alkyl or together with R_2 and the nitrogen atom forms a 5- to 7-membered ring which is unsubstituted or substituted by an alkoxy carbonyl 20 group of up to 6 carbon atoms or by one or two

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alkyl groups each having 1 to 4 carbon atoms, and

R₂ represents a straight-chain or branched C₁-C₂₂-alkyl, C₇-C₁₂-aralkyl, C₃-C₁₀-cycloalkyl, C₆-C₁₄-aryl or a terpenyl radical, each of which is unsubstituted or substituted by halogen, alkyl or alkoxy each having 1 to 4 C atoms.

2. A compound according to Claim 1, in which

R₁ represents alkyl of 1 to 4 C atoms, benzyl, cycloalkyl of 3 to 7 C atoms, phenyl, furyl, indolylmethyl, naphthyl, naphthylmethyl, thienyl or pyridyl, in which the alkyl and aryl radicals mentioned are unsubstituted or mono- or disubstituted by hydroxyl, methoxy, halogen, alkyl, cycloalkyl of up to 6 C atoms, phenoxy, benzoxy, acetylamino, benzyloxycarbonyl or alkoxycarbonyl of up to 4 C atoms,

R₃ represents hydrogen, methyl or ethyl or together with R₁ forms a tri- or tetramethylene group,

X represents oxygen or an NR₄ group, in which

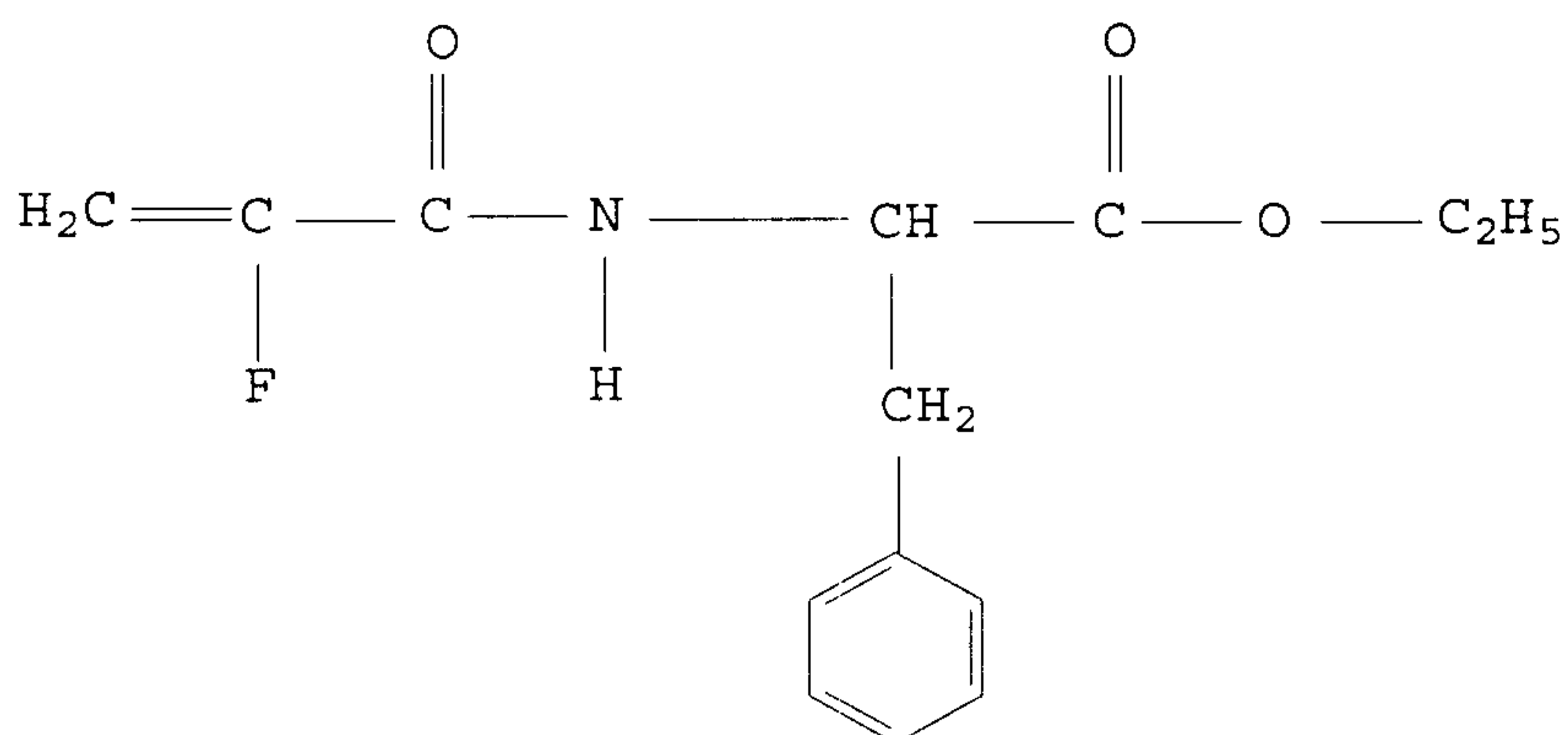
R₄ represents hydrogen or alkyl of 1 to 4 C atoms or together with R₂ and the nitrogen atom forms a 5- to 7-membered ring which is unsubstituted or substituted by alkyl or alkoxycarbonyl each having up to 4 C atoms, and

R₂ represents alkyl of up to 12 C atoms, benzyl, cycloalkyl of 3 to 7 C atoms, phenyl or terpenyl, in which the radicals mentioned are unsubstituted or substituted by fluorine, chlorine or bromine or by alkyl or alkoxy each having up to 2 C atoms.

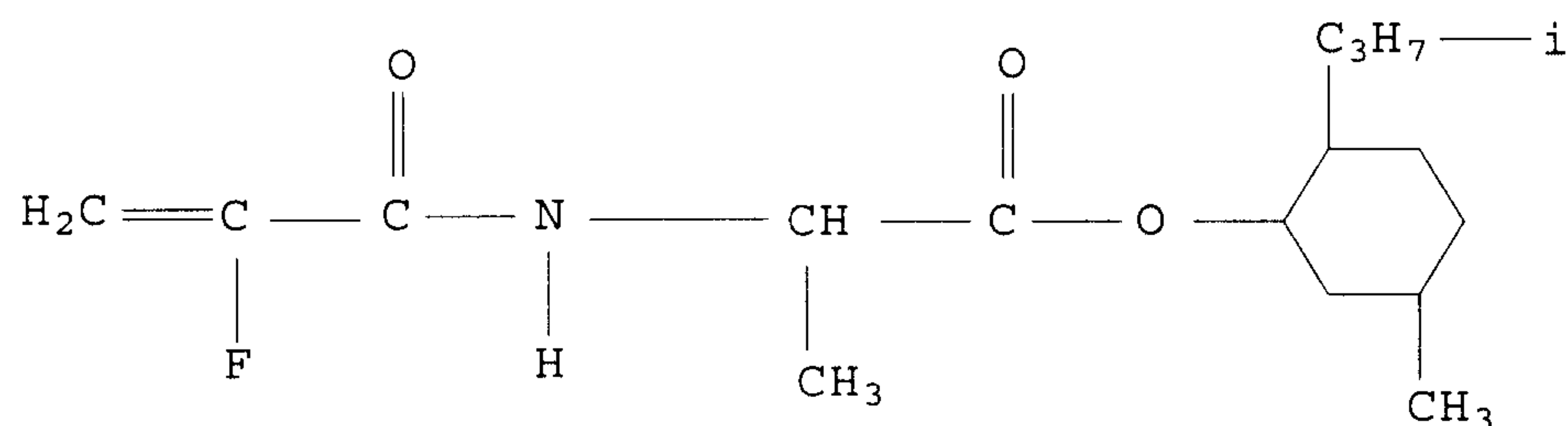
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3. A compound according to Claim 1, containing a residue of an optically active amino acid selected from the group consisting of alanine, aminobutyric acid, valine, norvaline, leucine, isoleucine, terleucine, phenylglycine, naphthylglycine, phenylalanine, thienylalanine, pyridylalanine, naphthylalanine, cyclohexylglycine, cyclohexylalanine, tyrosine, tryptophan, serine, aspartic acid, glutamic acid, ornithine, lysine, proline and 6-aminopenicillanic acid.

10 4. A compound according to Claim 1, wherein such compound is N-fluoroacryloyl-L-phenylalanine ethyl ester of the formula

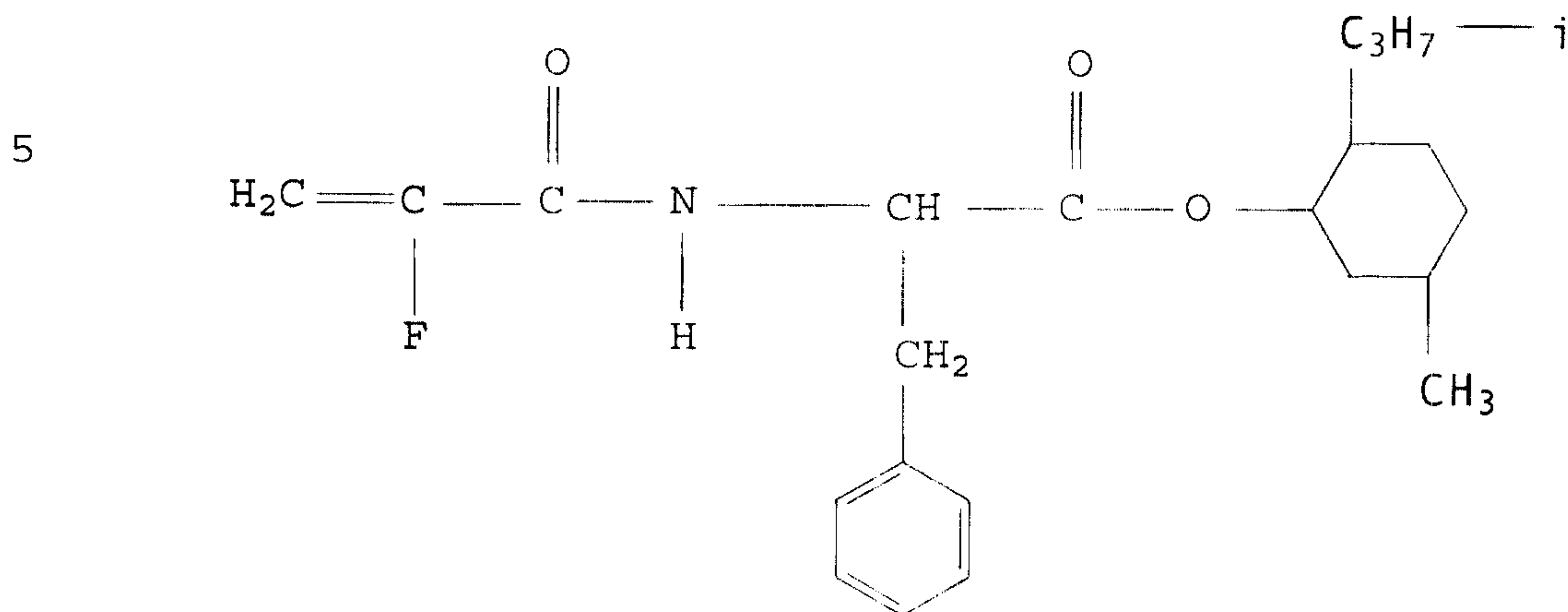


5. A compound according to Claim 1, wherein such compound is N-fluoroacryloyl-L-alanine d-menthyl ester of the formula

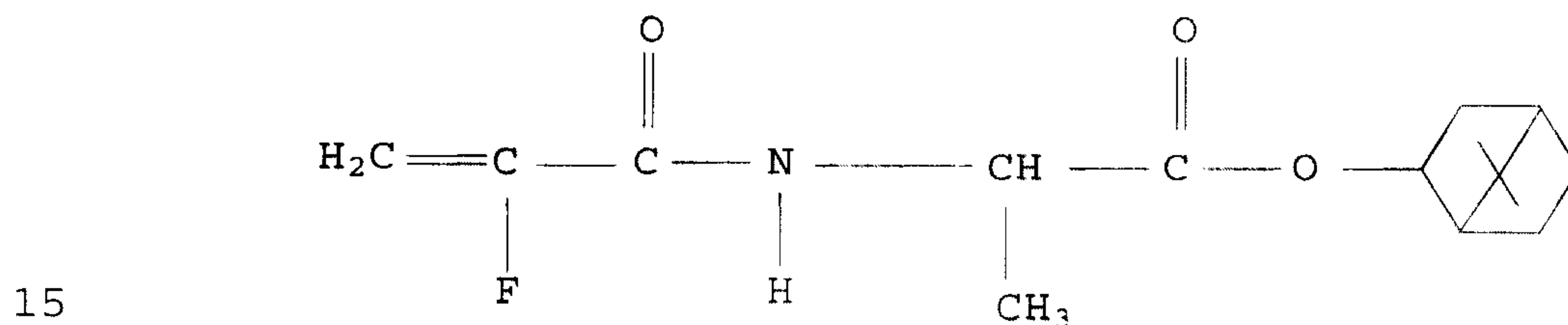


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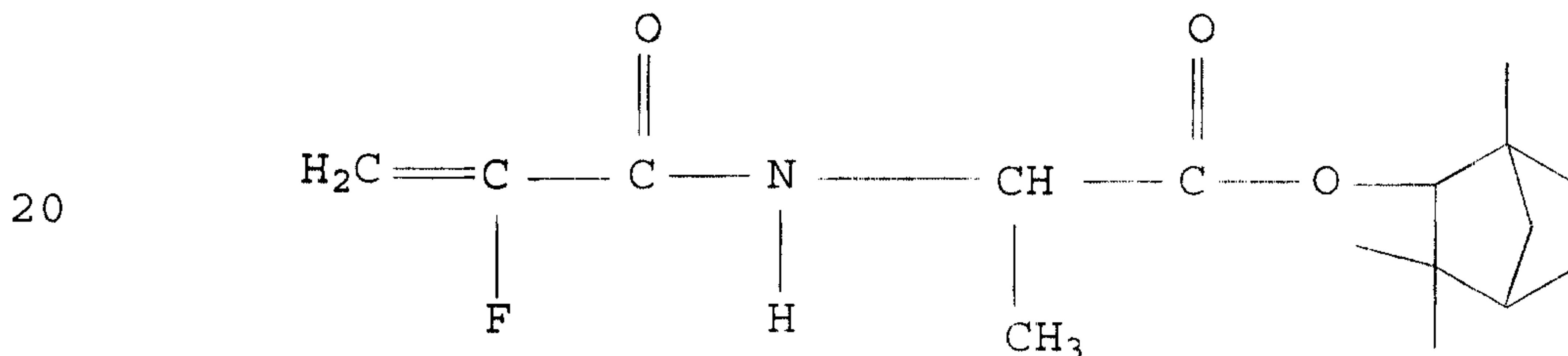
6. A compound according to Claim 1, wherein such compound is N-fluoroacryloyl-L-phenylalanine d-menthyl ester of the formula



10 7. A compound according to Claim 1, wherein such compound is N-fluoroacryloyl-L-alanine 1-bornyl ester of the formula

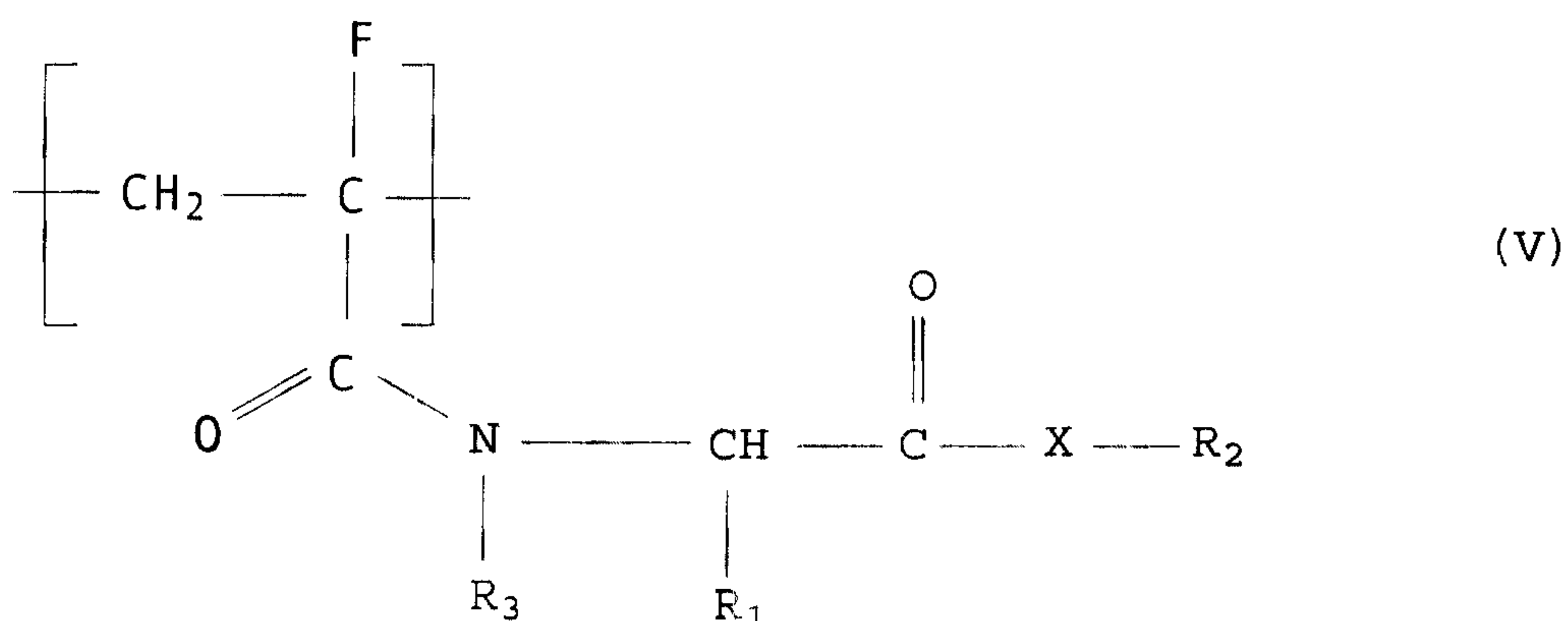


8. A compound according to Claim 1, wherein such compound is N-fluoroacryloyl-L-alanine (+)-fenchyl ester of the formula



9. An optically active polymer containing at least 40 mol% of structural units of the formula (V)

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in which

R_1 represents a straight-chain or branched C_1 - C_8 -alkyl, a C_7 - C_{12} -aralkyl, a C_3 - C_{10} -cycloalkyl, a C_6 - C_{14} -aryl or a furyl, thienyl or pyridyl radical, which are unsubstituted or substituted by benzyloxycarbonyl, alkoxycarbonyl of up to 6 C atoms, hydroxyl, alkyl, cycloalkyl or alkoxy each having up to 6 C atoms, halogen, phenoxy, benzoxy, acylamino of up to 8 C atoms or by carbonylalkoxy of up to 6 C atoms,

R_3 represents hydrogen or C_1 - C_4 -alkyl or together with R_1 forms a tri- or tetramethylene group,

X is oxygen or an NR_4 group, in which

R_4 represents hydrogen or straight-chain or branched C_1 - C_4 -alkyl or together with R_2 and the nitrogen atom forms a 5- to 7-membered ring which is unsubstituted or substituted by an alkoxycarbonyl group of up to 6 carbon atoms or by one or two alkyl groups each having 1 to 4 carbon atoms, and

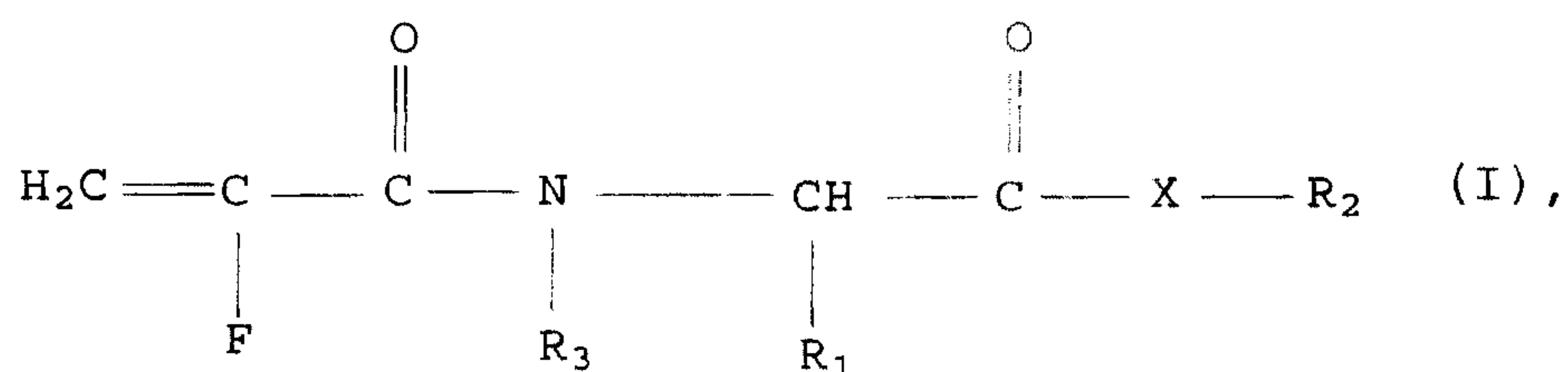
R_2 represents a straight-chain or branched C_1 - C_{22} -alkyl, C_7 - C_{12} -aralkyl, C_3 - C_{10} -cycloalkyl, C_6 - C_{14} -aryl or a terpenyl radical, each of which is unsubstituted or

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substituted by halogen, alkyl or alkoxy each having 1 to 4 C atoms.

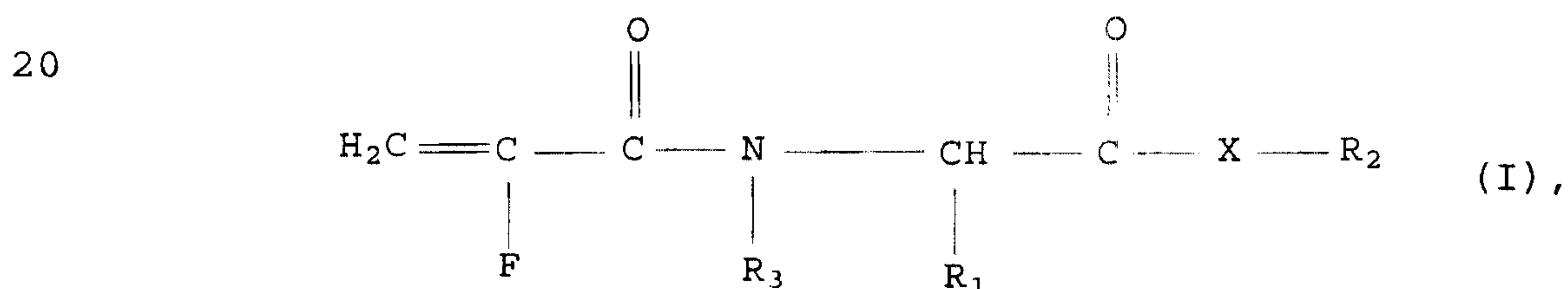
10. An optically active polymer according to Claim 9, in the form of a crosslinked insoluble or swellable bead polymer or in a form in which it is bound to a finely divided inorganic support material.

11. A process for the preparation of a crosslinked bead polymer according to Claim 10, which comprises polymerising an N- α -fluoroacryloylamino acid derivative of the formula



wherein R_1 , R_2 and X are as defined in Claim 9, in the presence of 0.5 to 50 mol% of a crosslinking agent.

12. A process for the preparation of an optically active polymer according to Claim 10, bound to an inorganic support material, which comprises polymerising a compound of the formula



wherein R_1 , R_2 and X are as defined in Claim 9, in the presence of a vinyl/silica gel or of an unsubstituted or (meth)acryloyl-substituted silica gel/diol phase.

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13. A method of resolving a mixture of optical isomers which comprises contacting said mixture with an optically active polymer according to Claim 9 or 10 and eluting the individual isomers from said polymer.

5 14. Use of an optically active polymer according to Claim 9 or 10 to resolve a mixture of optical isomers.

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FIG. 1

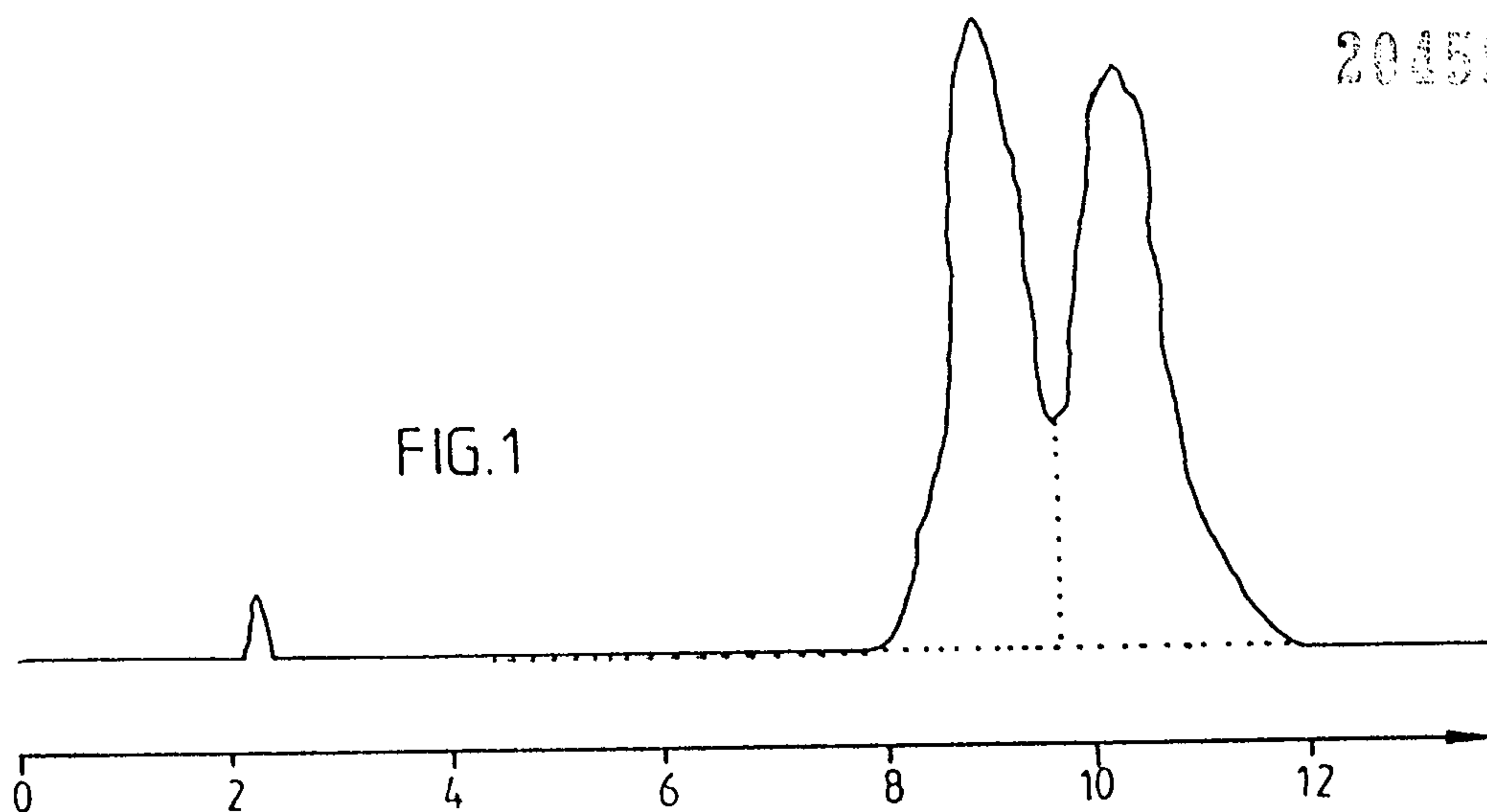


FIG. 2

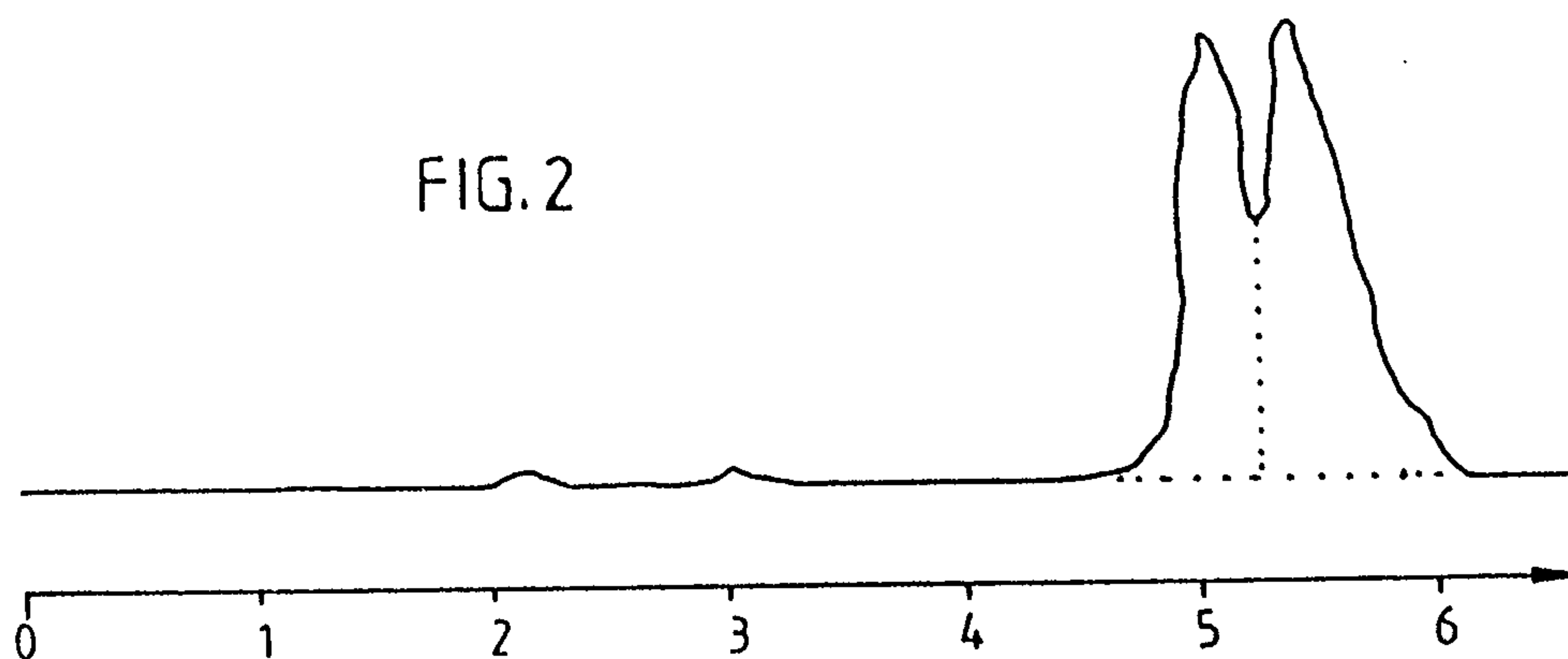
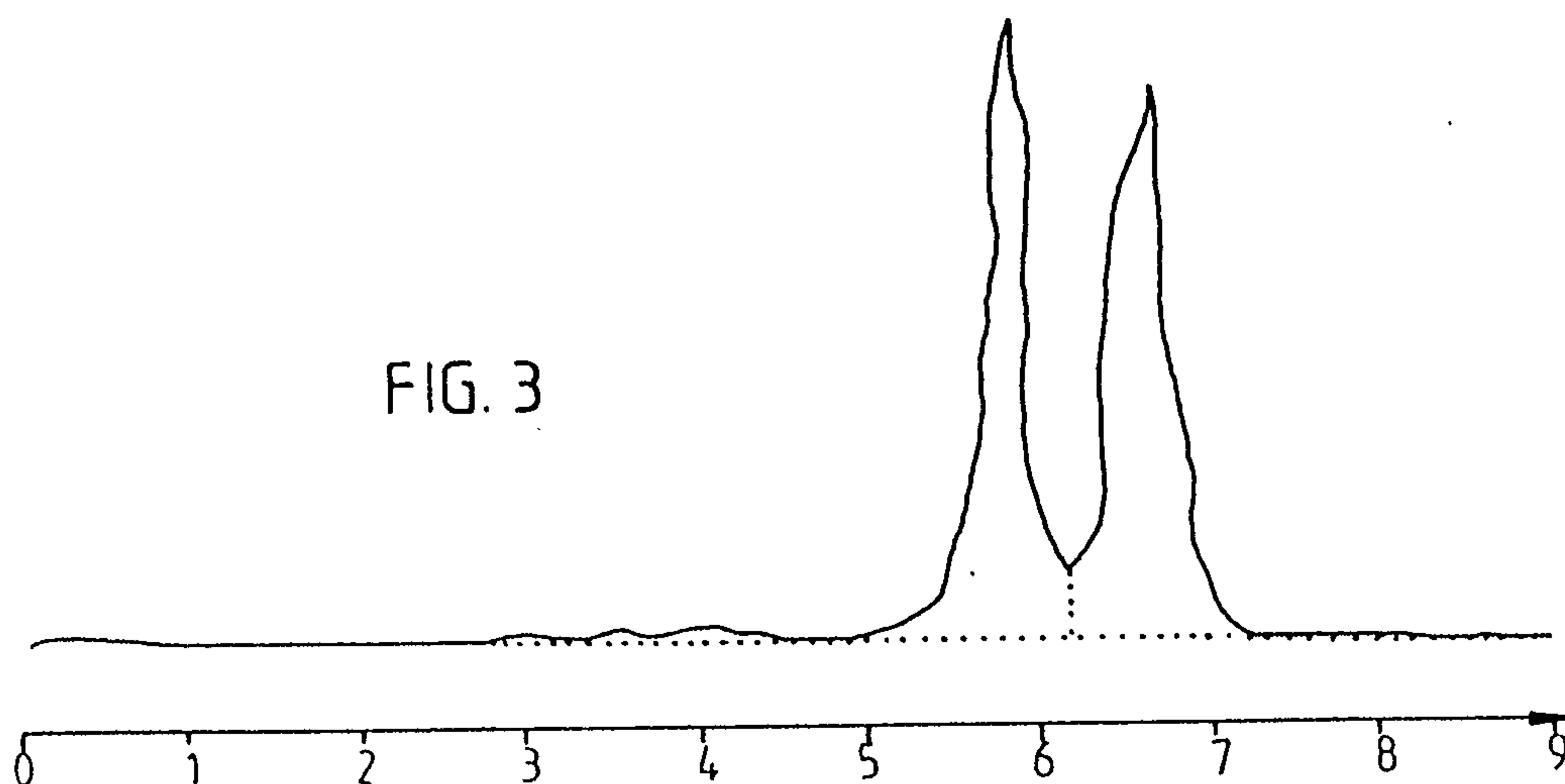
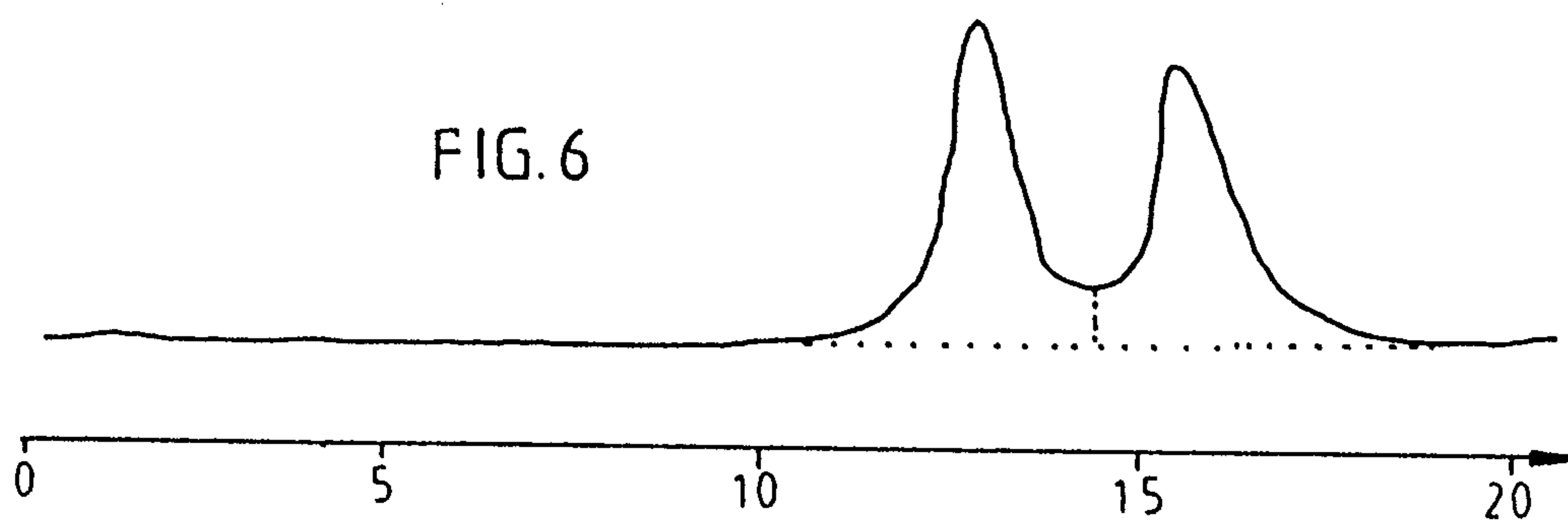
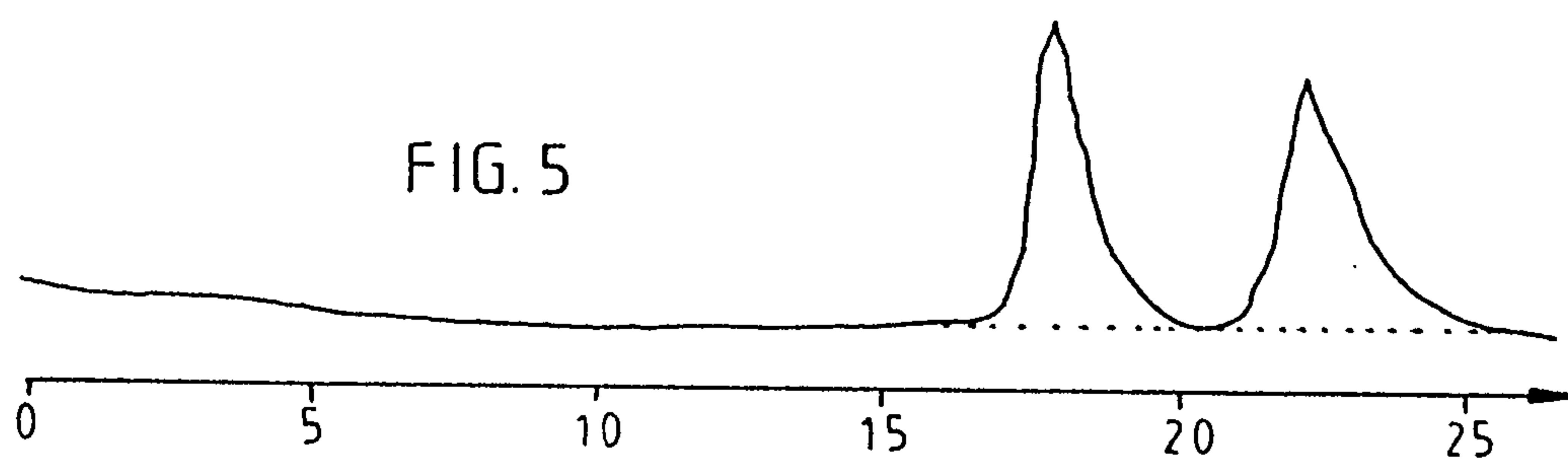
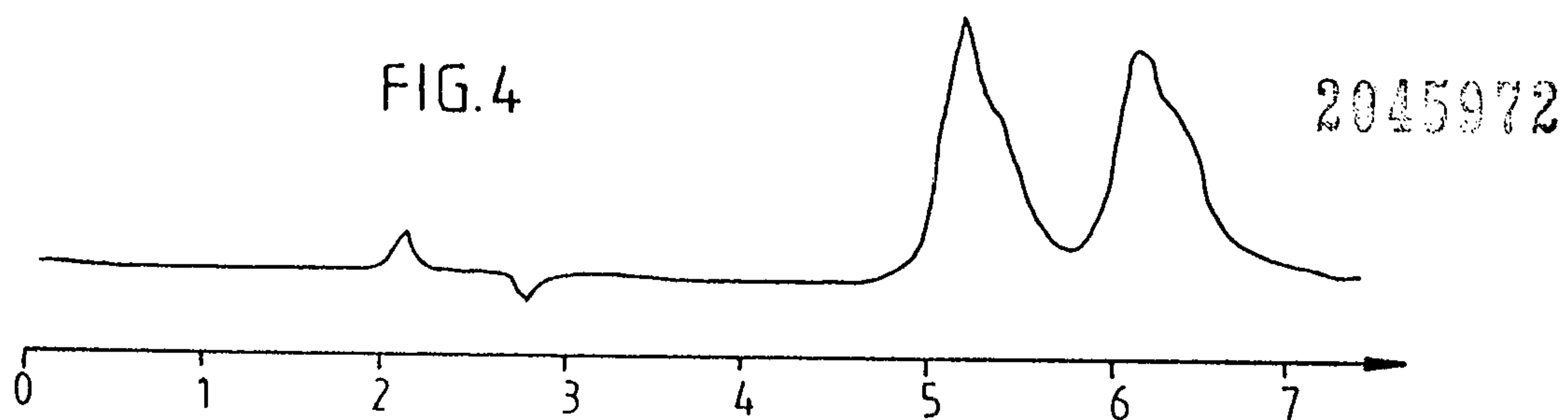


FIG. 3



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FIG. 7

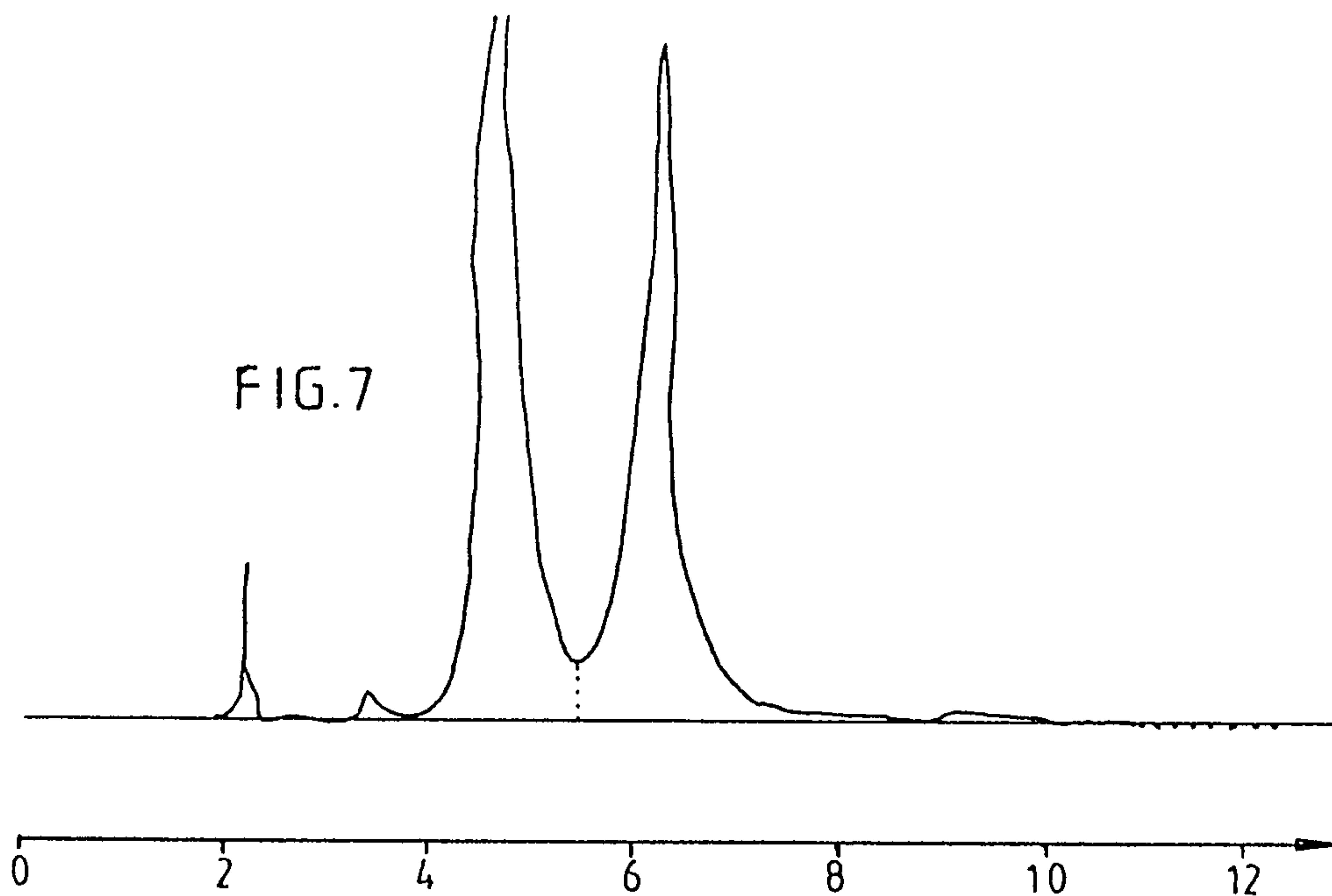
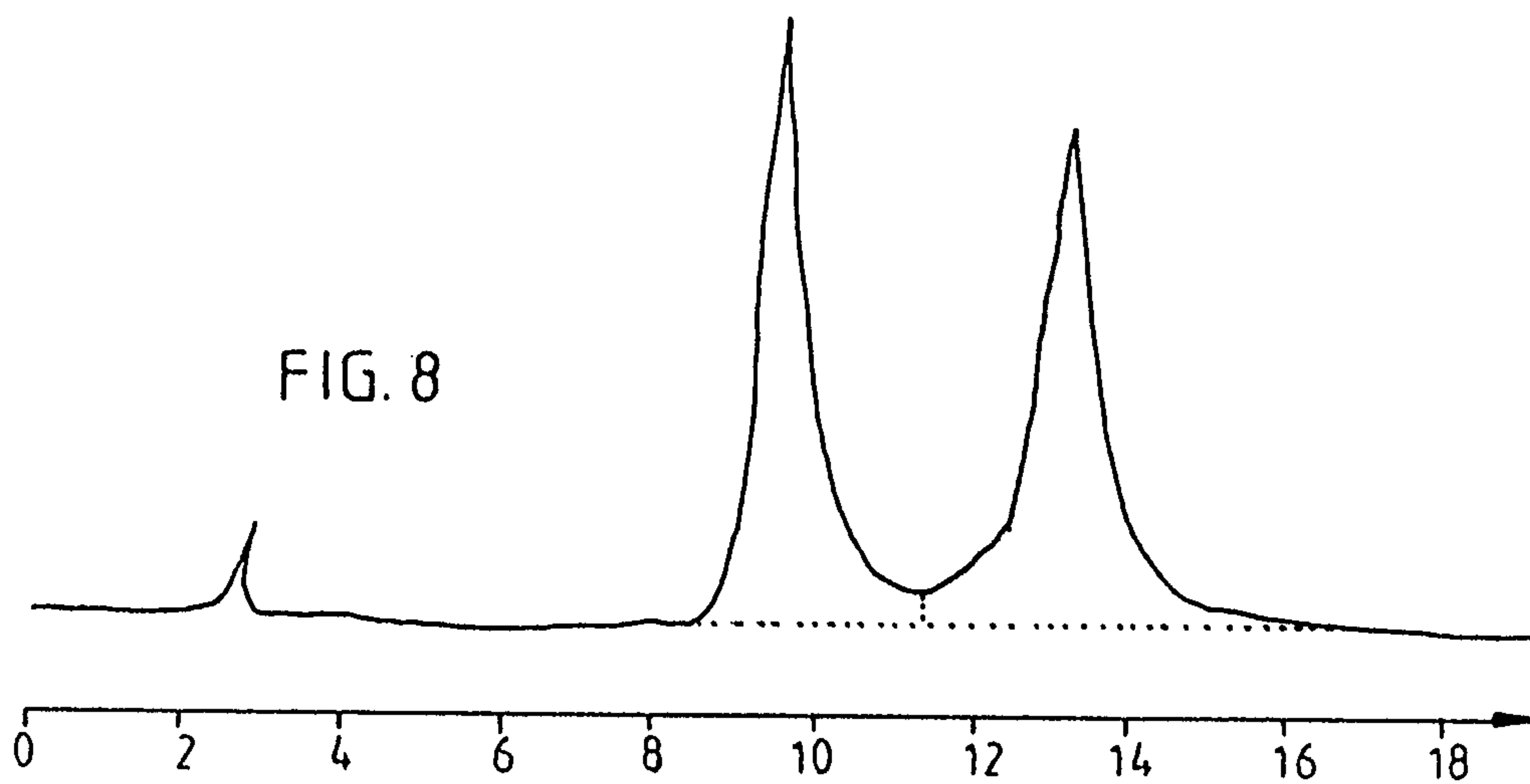
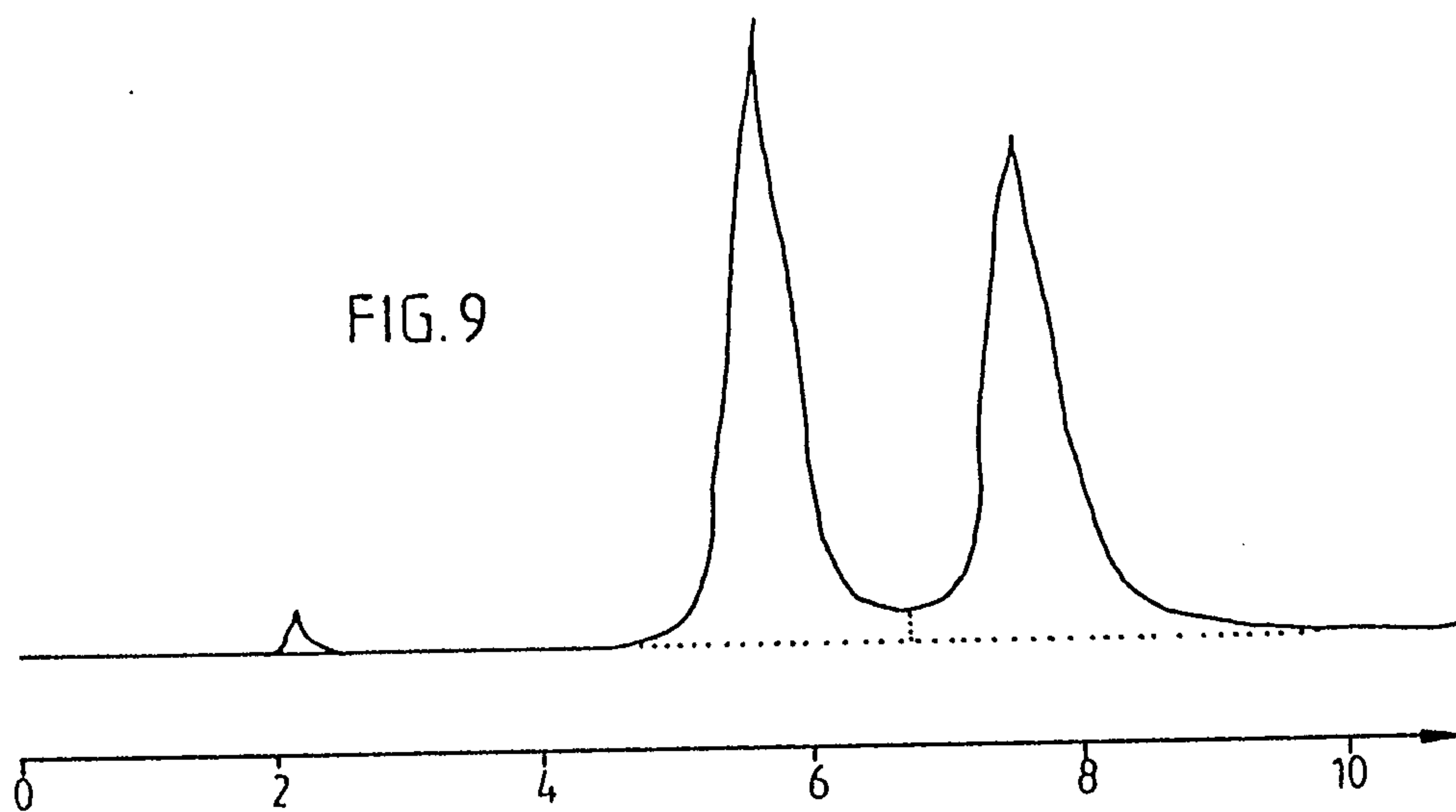


FIG. 8



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